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Patent Abstracts of Japan

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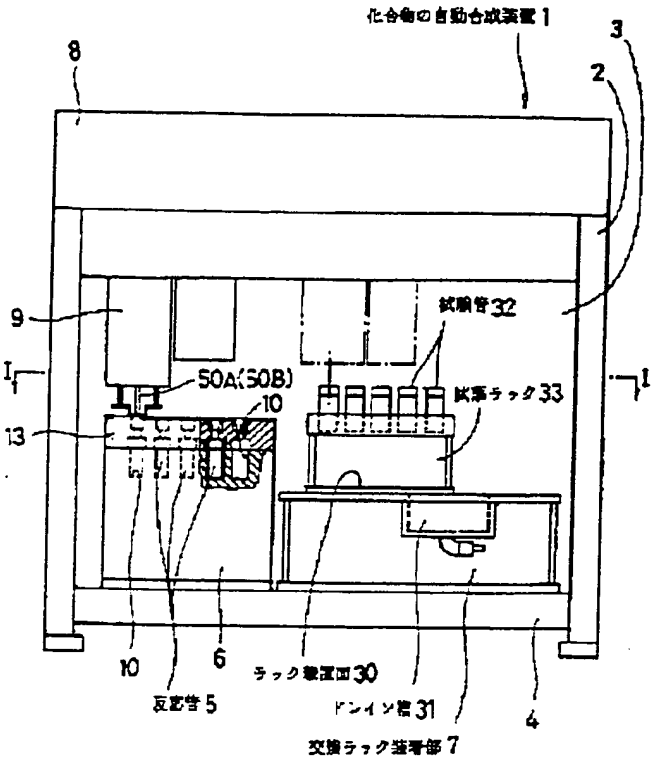
APPLICATION NUMBER : 09238644

APPLICANT : MORITEX CORP;

INVENTOR : KOIKE TOSHIO;

INT.CL. : C07B 61/00 C09K 3/10

TITLE : COMPOUND AUTOMATICALLY SYNTHESIZING APPARATUS AND SEALING STRUCTURE FOR REACTION TUBE USED THEREFOR



ABSTRACT : PROBLEM TO BE SOLVED: To provide the subject apparatus capable of automatically carrying out various operations required for synthesis of compound, being constituted extremely compactly and simply, omitting the uselessness of installation space and greatly reducing a production cost.

SOLUTION: This apparatus comprises a reagent rack 33 which is equipped with a chemical injecting needle 50A to be moved and controlled between a reaction block 6 provided with a stirring means for forming a rotary magnetic field by rotating a magnet sunk in each reaction tube 5 and with a temperature control means for heating or cooling each reaction tube 5 and an exchange rock fitting part 7 so as to freely determine a position and is furnished with arranged test tubes 33 for preserving each fixed amount of the reagent on the exchange rack fitting part 7, a sample rack provided with arranged test tubes for storing each fixed amount of a compound having finished a reaction, a filtration rack provided with arranged cartridges with a filter for injecting a fixed amount of the compound having finished reaction and filtering or a column purifying rack provided with extraction tubes for purifying the compound having finished reaction by columns. These racks are exchanged and fixed.

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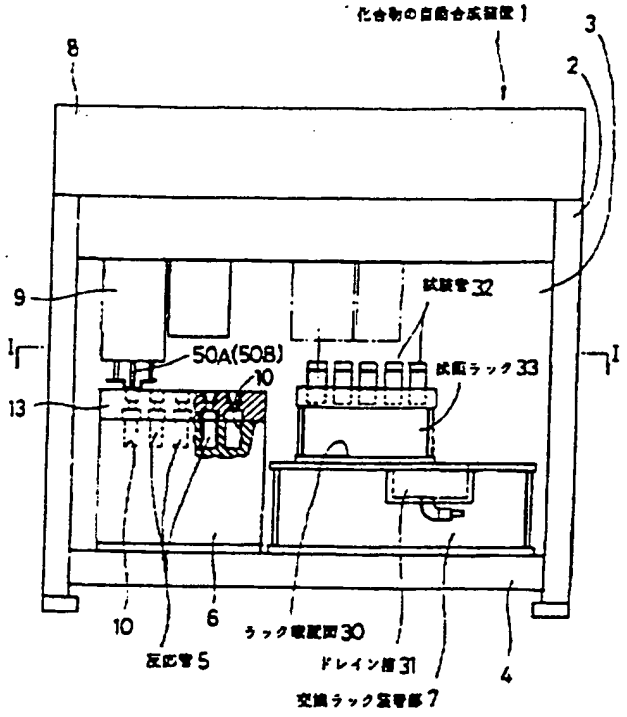
(54)【発明の名称】　化合物の自動合成装置とこれに用いる反応管のシール構造

(57)【要約】

【課題】　化合物を合成する際に必要な種々の操作を自動的に行うことができるだけでなく，極めてコンパクトで簡素な構成にして設置スペースの無駄を省き，製造コストを大幅に軽減する。

【解決手段】　各反応管(5)内に沈めた磁石(5c)を回転させる回転磁場を形成する撹拌手段（11）及び各反応管(5)を加温又は冷却する温度制御手段(12)を備えた反応ブロック(6)と、交換ラック装着部(7)との間を位置決め自在に移動制御される薬液注入ニードル(50A)を備え、前記交換ラック装着部(7)に、試薬を所要量ずつ貯留する試験管(32)が配列された試薬ラック(33)、反応終了した化合物を所要量ずつ貯留する試験管(34)が配列されたサンプルラック(35)、反応終了した化合物を所要量ずつ注入して沪過するフィルタ付の沪過カートリッジ(36)を配列した沪過ラック(37)、または、反応終了した化合物をカラム精製する抽出管(38)を配列したカラム精製ラック(39)を交換して装着できるようにした。



1

【特許請求の範囲】

【請求項1】　試薬ラック（33）に配列された各試験管（32）の位置と反応ブロック（6）に配列された各反応管（5）の位置に位置決め可能に移動制御される薬液注入ニードル（50A，50B）で、前記各試験管（32）内に貯留された試薬を吸入して前記各反応管（5）に所要量ずつ注入し、当該各反応管（5）ごとに任意の混合率の化合物を合成する化合物の自動合成装置において、

前記反応ブロック（6）は、各反応管（5）の周方向に回転する回転磁場を形成して反応管（5）内に沈めた磁気撹拌子（5c）を回転させる撹拌手段（11）と、各反応管（5）を加温又は冷却する温度制御手段（12）を備え、前記試薬ラック（33）は交換ラック装着部（7）に着脱自在に装着され、

前記交換ラック装着部（7）は、前記試薬ラック（33）に換えて、反応終了した化合物を所要量ずつ貯留する試験管（34）が配列されたサンプルラック（35）、反応終了した化合物を所要量ずつ注入して沪過するフィルタ付きの沪過カートリッジ（36）を配列した沪過ラック（37）、または、反応終了した化合物をカラム精製する抽出管（38）を配列したカラム精製ラック（39）のいずれかが装着可能に形成されたことを特徴とする化合物の自動合成装置。

【請求項2】　前記反応ブロック（6）の温度制御手段（12）は、各反応管（5）を加熱するヒータ（16）と、各反応管（5）を冷却する冷媒を外部循環させる流通路（17）からなる請求項1記載の化合物の自動合成装置。

【請求項3】　前記交換ラック装着部（7）は、ラックを載置するラック載置面（30）の左右片側にドレイン槽（31）が形成されてなる請求項1記載の化合物の自動合成装置。

【請求項4】　前記交換ラック装着部（7）は、ラックを載置するラック載置面（30）の左右片側にドレイン槽（31）が形成され、前記カラム精製ラック（39）は、前記抽出管（38）からの溶出液を回収する試験管（43）を配列したフラクションラック（44）が前記ラック載置面（30）のドレイン槽（31）のない部分に載置されると共に、反応終了したサンプルをカラム精製する抽出管（38）を配列したシフトラック（45）が前記フラクションラック（44）の上方で水平方向にスライド可能に配されてなり、当該シフトラック（45）は、一端側にスライドさせたときに前記フラクションラック（44）の上方に位置決めされ、他端側にスライドさせたときにドレイン槽（31）の上方に位置決めされるように形成されて成る請求項1記載の化合物の自動合成装置。

【請求項5】　前記交換ラック装着部（7）は、前記試薬ラック（33）に換えて、薄層クロマトグラフィーの固定層を形成したＴＬＣ基板（60）を略水平に支持するＴＬＣ基板支持ラック（61）が装着可能に形成されてなる請求項1記載の化合物の自動合成装置。

2

【請求項6】　薬液注入ニードル（50A，50B）で複数の試薬を所要量ずつ注入して任意の混合率の化合物を合成する反応管（5）の上端開口部（59）に、前記ニードル（50A，50B）を挿通する透孔（56）が形成されたアルミキャップ（5b）が螺合されると共に、当該アルミキャップ（5b）と反応管（5）の上端開口部（59）との隙間に弾性パッキン（5a）が挟装され、当該弾性パッキン（5a）はシリコンゴム（57）で形成されると共に、その底面にフッ素樹脂フィルムのライニング（58）が施されたことを特徴とする反応管のシール構造。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、反応ブロックに配列された各反応管ごとに任意の混合率の化合物を合成する化合物の自動合成装置及びこれに用いる反応管のシール構造に関する。

【０００２】

【従来の技術】最近では、いくつかの物質を組み合わせて新規な化合物をつくり出す場合に、コンビナトリアルケミストリーという手法が採られている。これは、予め用意した数種類の試薬を、各試験管ごとに夫々任意の混合率で混合することにより、混合率が異なる多数のサンプルを合成し、その中から最適の混合率を有する化合物を選び出すものである。具体的には、まず、ラックに配列された多数の反応管ごとに任意の混合率で試薬を注入する試薬注入操作を行い、次いで、反応管に注入された試薬を撹拌し温度制御して所定の化学反応を進行させる反応操作を行う。そして、反応が終了して合成された化合物が複数の液層に分かれている場合は所定の液層部分から化合物を吸入する分液操作を行い、反応が終了した化合物を沪過する必要がある場合は沪過操作を行い、反応が終了した化合物を分析するためにカラム精製操作を行うなどの各種操作が必要になる。

【０００３】　この場合、非常に多数のサンプルを合成し、その夫々について上述の処理を行わなければならないので、最近では試薬注入装置，反応装置，分液装置，沪過装置，カラム精製装置などを用いて各処理を自動的に行うようにしている。これによれば、まず、試薬注入装置で各反応管に対して所定の混合率で試薬が注入される。次いで、反応装置では、化学反応を行う温度条件，時間条件，撹拌条件などの各条件が予めプログラムされているので、所定の混合率で試薬が注入された各反応管を反応装置にセットしさえすれば、そのプログラム通りに反応が進行する。そして、反応が終了した化合物が複数の液層に分かれている場合は、これを分液装置にかければ、所定の液層部分から所望の化合物を取り出すことができ、さらに必要がある場合は反応管内の化合物を沪過装置にかけて沪過した後、カラム精製装置で分析の前処理を行うことができる。

【０００４】

【発明が解決しようとする課題】しかしながら、このような自動機を用いた場合に、各操作は自動化されているものの、一台につき一操作しか行うことができないので、各操作ごとに自動機を設置しなければならず、コストが高み設置スペースが無駄になるという問題があった。また、これらの各操作を一台で行わせようとする場合に、単に各装置を寄せ集めただけでは製造コストはそれ程軽減されることもなく、その一台が大型化するため設置スペースが節約されることもない。

【０００５】　そこで本発明は、化合物を合成する際に必要な種々の操作を自動的に行うことができるだけでなく、極めてコンパクトにして設置スペースの無駄がなく、製造コストを大幅に軽減することを技術的課題としている。

【０００６】

【課題を解決するための手段】この課題を解決するために、本発明は、試薬ラックに配列された各試験管の位置と反応ブロックに配列された各反応管の位置に位置決め可能に移動制御される薬液注入ニードルで、前記各試験管内に貯留された試薬を吸入して前記各反応管に所要量ずつ注入し、当該各反応管ごとに任意の混合率の化合物を合成する化合物の自動合成装置において、前記反応ブロックは、各反応管の周方向に回転する回転磁場を形成して反応管内に沈めた磁気撹拌子を回転させる撹拌手段と、各反応管を加温又は冷却する温度制御手段を備え、前記試薬ラックは交換ラック装着部に着脱自在に装着され、前記交換ラック装着部は、前記試薬ラックに換えて、反応終了した化合物を所要量ずつ貯留する試験管が配列されたサンプルラック、反応終了した化合物を所要量ずつ注入して沪過するフィルタ付きの沪過カートリッジを配列した沪過ラック、または、反応終了した化合物をカラム精製する抽出管を配列したカラム精製ラックのいずれかが装着可能に形成されたことを特徴とする。

【０００７】　本発明によれば、交換ラック装着部に、試薬ラック，サンプルラック，沪過ラック，カラム精製ラックが夫々交換可能に装着される。したがって、試薬注入操作を行う場合は試薬ラックを装着すれば、薬液注入ニードルで試薬ラックの各試験管内に貯留された試薬が吸入されて反応ブロックに配列された各反応管に注入される。次いで、反応ブロックは、各反応管内に沈めた磁石を回転させる回転磁場を形成する撹拌手段と、各反応管を加温又は冷却する温度制御手段を備えているので、その場で、反応管に注入された試薬を撹拌し温度制御して所定の化学反応を進行させる反応操作が行われる。

【０００８】　そして、分液操作を行う場合は、交換ラック装着部にサンプルラックを装着して、薬液注入ニードルで反応管の所定の液相から化合物を吸入し、サンプルラックの試験管に吐出させればよい。また、沪過操作を行う場合は、交換ラック装着部に沪過ラックを装着して、反応ブロックに配列された反応管又は反応ブロック上に載置したサンプルラックに配列された試験管から薬液注入ニードルで吸入した化合物を、沪過ラックの沪過カートリッジ内に吐出させればよい。さらに、カラム精製操作を行う場合は、交換ラック装着部にカラム精製ラックを装着し、薬液注入ニードルで吸入した化合物をカラム精製ラックの抽出管内に吐出させればよい。このように交換ラック装着部に装着するラックを交換するだけで、一台の装置で各操作を自動的に行うことができるので、装置自体を極めてコンパクトに形成することができ、製造コストも低減される。

【０００９】

【発明の実施の形態】以下、本発明の実施の形態を図面に基づいて具体的に説明する。図１は本発明に係る化合物の自動合成装置を示す正面図、図２は図１のＩ－Ｉ線断面図、図３は反応ブロックの内部構造を示す拡大図、図４は交換ラック装着部にサンプルラックを装着した状態を示す正面図、図５は交換ラック装着部にＴＬＣ基板支持ラックを装着した状態を示す正面図、図６は交換ラック装着部に沪過ラックを装着した状態を示す正面図、図７は交換ラック装着部にカラム精製ラックを装着した状態を示す正面図、図８は配管系を示す流体回路図、図９は反応管とサンプリングニードルを示す拡大図、図１０は抽出管とカラム精製ニードルを示す拡大図である。

【００１０】　本例の化合物の自動合成装置１は、ボックス形の本体２の手前に透明の扉３が取り付けられており、扉３を開くと本体２のベース４には、例えば、正面左手に容積５ｃｃの反応管５，５を配列した反応ブロック６が配設されると共に、正面右手には各種のラックを着脱可能に装着する交換ラック装着部７が形成されている。また、本体天井部８には、直交３軸方向に移動制御されるロボットアーム９が配設され、反応ブロック６に配列される反応管５の位置や交換ラック装着部７に装着したラックに配列される試験管の位置に位置決めされるように成されている。

【００１１】　反応管５は、その上端開口部５９に、シリコンゴムとフッ素樹脂フィルムの二層構造に形成された弾性パッキン５ａを有するキャップ５ｂが装着され、その内部には、両端にＮ－Ｓ極を形成した磁気撹拌子５ｃが沈められている。より具体的には、反応管５の上端開口部５９に、後述する薬液注入ニードル５０Ａ，５０Ｂを挿通する透孔５６が形成されたアルミキャップ５ｂが螺合されると共に、当該アルミキャップ５ｂと反応管５の上端開口部５９との隙間に弾性パッキン５ａが挟装されている。この弾性パッキン５ａは、ＪＩＳ－Ａ型硬さ試験機で測定した硬さＨｓＡ＝２０～２５程度のジメチルシリコンゴム５７で形成されると共に、その底面に厚さ１００μｍ程度のフッ素樹脂フィルムのライニング５８が施されている。このフッ素樹脂フィルムとしては，例えば、テトラフルオロエチレン－ヘキサフルオロ

プロピレン共重合体のフィルムが用いられている。

【0012】　反応ブロック6は、その上面に例えば容量5ccの反応管5を所定間隔でマトリクス状に配列する配列孔10・・が開口形成されると共に、その内部には、各配列孔10・・に反応管5・・を配置した状態で、当該各反応管5の周方向に回転する回転磁場を形成して反応管5内に沈めた磁気撹拌子5cを回転させる撹拌手段11と、各反応管5を加温又は冷却する温度制御手段12を備えている。また、当該反応ブロック6には、反応管5を装着した状態で加熱反応時にそのキャップ5b部分を冷却する冷却マニホールド13が取り付けられている。なお、この反応ブロック6も必要に応じて自動合成装置1から取り外すことができる。

【0013】　撹拌手段11は、各配列孔10の下方に配設された永久磁石14aを先端に取り付けた回転軸14の他端側にプーリ14bが取り付けられ、当該各プーリ14b・・にプラスチックベルト14cが掛け回されてモータ15により回転駆動されるようになされている。また、温度制御手段12は、配列孔10に配列された反応管5を加熱する電気ヒータ16と、各反応管5を冷却する冷媒を外部循環させる流通路17からなり、設定温度に応じてヒータ16を通電し、または、流通路17に冷媒を流通させるように成されている。

【0014】　さらに、冷却マニホールド13は、反応ブロック6に対して蝶番18を介して開閉可能に取り付けられ、各反応管5のキャップ5bを覆う凹部19を形成した冷却ブロック20が当該マニホールド13の底面側に配され、当該冷却ブロック20には冷媒を外部循環させる流通路21が形成されている。また、前記各凹部19は、後述するサンプリングニードル（薬液注入ニードル）50Aを挿し込む挿通孔22を介して上面側に開放され、前記挿通孔22は、所定間隔で配された2枚のシリコンゴムシート23A，23Bで塞がれると共に、各挿通孔22のゴムシート間が窒素ガス供給路24を介して連通されている。

【0015】　交換ラック装着部7は、各種ラックを載置するラック載置面30が形成されると共に、当該載置面30の左右片側にドレイン槽31が形成されている。そして、ラック載置面30には、試薬を貯留した複数の試験管32を配列する試薬ラック33、反応終了した化合物を所要量ずつ貯留する試験管34を配列するサンプルラック35、反応終了した化合物を所要量ずつ注入して沪過するフィルタ付きの沪過カートリッジ36を配列する沪過ラック37、反応終了した化合物をカラム精製する抽出管38を配列したカラム精製ラック39、または、反応中の化合物や反応終了した化合物を分析する薄層クロマトグラフィーに用いるTLC基板60を略水平に支持するTLC基板支持ラック61が装着可能に形成されている。

【0016】　沪過ラック37は、試験管40を配列するラック本体41の上面に当該試験管40と等ピッチで沪過カートリッジ36を配列するカートリッジラック42が着脱自在に載置されて成り、沪過カートリッジ36はそのフィルタ36a部分のみを交換することができるように形成されている。

【0017】　カラム精製ラック39は、試験管43を配列したフラクションラック44がラック載置面30のドレイン槽31のない部分に載置されると共に、反応終了した化合物をカラム精製する抽出管38を配列したシフトラック45が前記フラクションラック44の上方で水平方向にスライド可能に配されて成り、当該シフトラック45を一端側にスライドさせたときに前記フラクションラック44の真上に位置決めされ、他端側にスライドさせたときにドレイン槽31の真上に位置決めされるように形成されている。

【0018】　TLC基板支持ラック61に支持されるTLC基板60は、例えば、シリカゲル，アルミナ，セルロースなどの粉末吸着剤を焼セッコウなどと練り合わせてガラス基板やアルミニウム基板に固着させて形成され、薄層クロマトグラフィーの固定層となる薄層を形成している。そして、TLC基板60は、基板支持ラック61に載置可能な一枚の大判のものであっても、これを複数枚に分割した比較的小さなものであっても、また、一枚の大判のものを必要に応じて分割可能に形成したものであってもよい。

【0019】　また、ロボットアーム9には、反応管5内に薬液を注入したり、反応管5から薬液を吸入するサンプリングニードル（薬液注入ニードル）50Aと、カラム精製を行う際に抽出管38内に化合物や溶媒を注入するカラム精製ニードル（薬液注入ニードル）50Bが、交換可能に取り付けられる。このサンプリングニードル50Aは反応管5のキャップ5bに装着された弾性パッキン5aを突き刺して貫通することができるように尖って形成され、先端に薬液吸入及び注入を行う流路50aが開口されると共に、ニードル50Aを突き刺した状態で反応管5内の空気を外部に排出する排気流路50bが当該ニードル50Aの下端側及び上端側に開口して形成されている。なお、この場合に、薬液として塩酸，硫酸等の酸性薬液を注入する場合は、少なくとも流路50aを形成する部分がハステロイCなどの耐酸性金属を用いて形成したサンプリングニードル50Aを用いる。また、カラム精製ニードル50Bは、内部に充填剤38aを充填した抽出管38の上端に嵌め込まれたキャップ38bの凹部38cに密接するように先端が球面状に形成されている。

【0020】　そして、ロボットアーム9は、薬液を吸入・吐出させたり溶媒を注入する配管系51を備え、当該配管系51は、その一端に前記ニードル50A，50Bに接続されるポート52が形成されると共に、他端に切換弁CVを介して複数の溶媒ボトルM_1～M_nが切換

接続され、吸入・吐出方向の切換可能な流量制御ポンプとしてデジタル制御シリンジポンプ５３が介装されてなる。したがって、このサンプリングニードル５０Ａを用いて、試薬ラック３３に配列された試験管３２から所要量の試薬を吸入して反応ブロック６に配列された反応管５内に所定量ずつ吐出させたり、溶媒ボトルM_1～Mnから溶媒を反応管５内に所定量ずつ吐出させたり、反応管５内で反応終了した化合物を吸入してサンプルラック３５に配列された試験管３４や、沪過ラック３７に配列された沪過カートリッジ３６に吐出させることができる。また、カラム精製ニードル５０Ｂを用いて、カラム精製ラック３９に配列された抽出管３８に、溶媒ボトルM_1～Mnから所定の溶媒を所定量吐出させたり、反応終了した化合物を吸入して所要量ずつ吐出させることができる。

【００２１】　なお、５４Ａ，５４Ｂは、前記各ニードル５０Ａ，５０Ｂを収容するニードルホルダであって、その内部にはニードル５０Ａ，５０Ｂの先端に洗浄液や加圧空気を吹き付ける洗浄装置（図示せず）が設けられている。また、５５は沪過する際に、沪過カートリッジ３６内に窒素ガスを加圧充填する多連加圧ノズルである。

【００２２】　以上が本発明の一構成例であって、次にその作用について説明する。化合物を合成する際には、例えば、①試薬注入操作，②溶媒注入操作，③反応操作，④ＴＬＣ分析操作，⑤分液サンプリング操作，⑥沪過操作，⑦カラム精製操作が行われるのでこれらについて説明する。

【００２３】　試薬注入操作は、反応ブロック６に配列された各反応管５ごとに任意の混合率の化合物を合成するために、試薬ラック３３に配列された各試験管３２内に貯留された試薬を吸入して前記各反応管５に所要量ずつ注入する操作である。この場合、まず、反応ブロック６の配列孔１０に反応管５を装着した後、冷却マニホールド１３でその上面を覆う。一方、交換ラック装着部７には、試薬を貯留した複数の試験管３２を配列した試薬ラック３３を装着する。この状態で、各反応管５ごとに試薬の注入量を設定すると、ロボットアーム９の先端にサンプリングニードル５０Ａが装着されて移動制御され、前記試験管３２内の試薬を吸入して各反応管５に所定量ずつ吐出する。その後、サンプリングニードル５０Ａがニードルホルダ５４Ａ内の洗浄装置で洗浄され、次いで、異なる試験管３２内の試薬が各反応管５に吐出され、これを繰り返して、必要な種類の試薬を反応管５ごとに任意の混合率で注入する。

【００２４】　次いで、必要に応じて溶媒注入操作を行う。これは化合物の合成に溶媒を使用する必要があるときに、各反応管５に所定量の溶媒を吐出させるもので、この場合は、各溶媒ボトルM_1～Mnから必要な溶媒をサンプリングニードル５０Ａを用いて各反応管５に注入する。なお、ここで、例えば、塩酸や硫酸などの酸性溶媒を注入する場合には、サンプリングニードル５０Ａとして、少なくともその内部流路５０ａが耐酸性金属で形成された耐酸ニードルを用いる。

【００２５】　このようにして、反応管５に複数の試薬を任意の混合率で注入した後、反応操作を行う。これは、撹拌・温度制御を行うことにより、所定の温度ー時間管理を行い予め設定された条件下で反応を進行させるものである。撹拌を行う場合は、撹拌手段１１のモータ１５を起動させれば、永久磁石１４ａが回転されるので、各配列孔１０ごとに回転磁界が形成され、反応管５内に沈められた磁気撹拌子５ｃが回転し、反応管５内の薬液が撹拌される。また、所定の温度制御を行う場合は、設定温度が室温以上の場合はヒータ１６に通電され、設定温度が室温以下の場合は外部から供給された冷媒が流通路１７内を循環し、所定の温度条件下で反応が進行される。

【００２６】　なお、反応管５を加熱する場合は、反応管５内の反応溶媒が外部に漏洩して反応液濃度が変化するおそれがある。そこで、この場合には、冷却マニホールド１３に形成された窒素ガス供給路２４から反応管５の周囲の隙間に窒素ガスを充填して反応管５を窒素ガス下に置き、この状態で流通路２１に冷媒を供給して反応管５のキャップ５ｂを冷却する。特に、キャップ５ｂとして、熱伝導率に優れたアルミ製のものを使用すれば、キャップ５ｂを冷却することにより、反応管５内の弾性パッキン５ａ及び上面開口部５９近傍が冷却される。これにより、反応管５内で蒸発された反応溶媒はキャップ５ｂで冷却されて結露し反応管５内に戻されるので、反応管５内の反応液濃度は変化しない。また、反応管５は窒素雰囲気下に置かれているので、その周囲、特にキャップ５ｂ上に結露を生ずることがなく、万一、結露したとしても、上面開口部５９が弾性パッキン５ａで気密状態に塞がれているので、内部に水滴が侵入することもない。なお、シリコンゴム５７の底面にフッ素樹脂フィルムのライニング５８を施してなる本例の弾性パッキン５ａを用いて、１００％メタノールを反応管５に入れ、キャップ５ｂを冷却しながら、２４時間加熱する実験を行ったところ、内容物の減少量は平均で0.18%程度と極めて良好なシール性が得られることが確認された。

【００２７】　次いで反応が終了した時点で、反応停止剤（例えば水）を注入して反応の進行を停止させ、必要に応じて、目的の化合物が精製されているか否かを確認したり、場合によっては反応が終了する前に反応中の生成物を確認するために、薄層クロマトグラフィーによるＴＬＣ分析操作を行う。このＴＬＣ分析操作は、合成された化合物が複数の液層に分液されている場合に、目的の化合物がどの液層で精製されているかを確認するために特に有益である。具体的には、試薬ラック３３を外して、ＴＬＣ基板支持ラック６１を装着し、当該ラック６

1に支持されたTLC基板60上に、各液層から所要量の化合物を滴下して、TLC基板60上に展開させた後、紫外線等を照射して分析する。

【0028】 そして、各反応管5内で合成された目的とする化合物を取り出す。この場合に、まず、交換ラック装着部7に装着された試薬ラック33又はTLC基板支持ラック61を外して、サンプルラック35を装着しておく。ここで、反応管5内で合成された化合物がコロイド状になって複数の液層に分液されていない場合は液層の位置を定める必要がないので、単に、反応管5内の化合物をサンプリングニードル50Aで吸入すればよい。また、合成された化合物が複数の液層に分液されている場合は分液サンプリングを行い、目的の化合物が精製されている液層部分の薬液を採取する。これは、反応管5内の液層の位置を設定することにより、サンプリングニードル50Aの先端をその液層内に位置させて吸入させ、吸入した化合物をサンプルラック35の試験管34に吐出させ、これを各反応管ごとに行なう。

【0029】 さらに、反応が終了した化合物について沪過する必要がある場合は、交換ラック装着部7のドレイン槽31の真上に位置するように沪過ラック37を装着する。そして、サンプルラック35の試験管34内に採取した化合物を沪過する場合は、サンプルラック35を反応ブロック6の上に載置し、サンプリングニードル50Aを用いて試験管34内の化合物を吸入して沪過カートリッジ36に注入する。また、反応管5から化合物を直接沪過カートリッジ36に注入する場合は、サンプリングニードル50Aを用いて反応管5内の化合物を吸入して沪過カートリッジ36に注入する。次いで、必要があれば、多連加圧ノズル55を用いて沪過カートリッジ36内に加圧窒素ガスを供給することにより、沪過時間を短縮できる。

【0030】 なお、合成された化合物の構造分析を行う前処理としてカラム精製操作を行う場合は、交換ラック装着部7にカラム精製ラック39を装着する。この場合、まず、フラクションラック44に試験管43を配列し、シフトラック45に抽出管38を配列して、当該シフトラック45をドレイン槽31側にスライドさせる。この状態で、ロボットアーム9の先端にカラム精製ニードル50Bを装着して、各抽出管38に所定の溶媒を注入しコンディショニングを行う。

【0031】 次いで、コンディショニングが終了すると、反応ブロック6の上に載置したサンプルラック35から吸入したサンプルを各抽出管38に注入するサンプルロードを行う。この場合、一のサンプルを一の抽出管38に注入するたびにカラム精製ニードル50Bの先端をニードルホルダ54B内の洗浄装置で洗浄することにより、サンプル同士が混ざるのを防止している。

【0032】 サンプルロードが終了すると抽出管38の固定層に保持されている夾雑物を洗い流す洗浄操作を行う。これは、カラム精製ニードル50Bにより洗浄溶剤を注入することにより行われ、そのとき抽出管38から流出される液はドレイン槽31に回収される。

【0033】 洗浄操作が終了すると、シフトラック45をフラクションラック44側に移動させて、抽出管38内に所定の溶媒を注入することにより溶出液をフラクションラック44の各試験管43に回収してカラム精製操作を終了する。なお、この場合に、抽出管38の溶出液を試験管43に直接回収するのではなく、溶出液を紫外線吸光度計でモニタして、溶出液に含まれる物質や溶出液の濃度を検出し、検出された物質や濃度が変化するたびごとに、フラクションラック44を移動させて自動的に新しい試験管43に交換し、紫外線吸収ピークのみを画分として自動分画を行ってもよい。そして、フラクションラック44の各試験管43内に回収された溶出液を遠心分離器にかけて濃縮し、これを溶解した後、構造分析装置にかければ構造分析を行うことができる。

【0034】

【発明の効果】 以上述べたように、本発明によれば、交換ラック装着部に装着されるラックを交換するだけで、試薬注入操作，合成反応操作，分液サンプリング操作，沪過操作，カラム精製操作など、化合物のパラレル合成に必要な各操作を一台の装置で自動的に行うことができ、装置自体を極めてコンパクトに形成することができ、製造コストを低減できるという大変優れた効果を奏する。

【図面の簡単な説明】

【図1】本発明に係る化合物の合成装置を示す正面図。

【図2】そのI－I線断面図。

【図3】反応ブロックの内部構造を示す拡大図。

【図4】交換ラック装着部にサンプルラックを装着した状態を示す正面図。

【図5】交換ラック装着部にTLC基板支持ラックを装着した状態を示す正面図。

【図6】交換ラック装着部に沪過ラックを装着した状態を示す正面図。

【図7】交換ラック装着部にカラム精製ラックを装着した状態を示す正面図。

【図8】配管系を示す流体回路図。

【図9】反応管とサンプリングニードルを示す拡大図。

【図10】抽出管とカラム精製ニードルを示す拡大図。

【符号の説明】

1・・・化合物の自動合成装置	5・・・反応管
5a・・弾性パッキン	5b・・キャップ
5c・・磁気撹拌子	6・・・反応ブロック
7・・・交換ラック装着部	11・・・撹拌手段
12・・・温度制御手段	16・・・ヒータ
17・・・流通路	30・・・ラック載置面

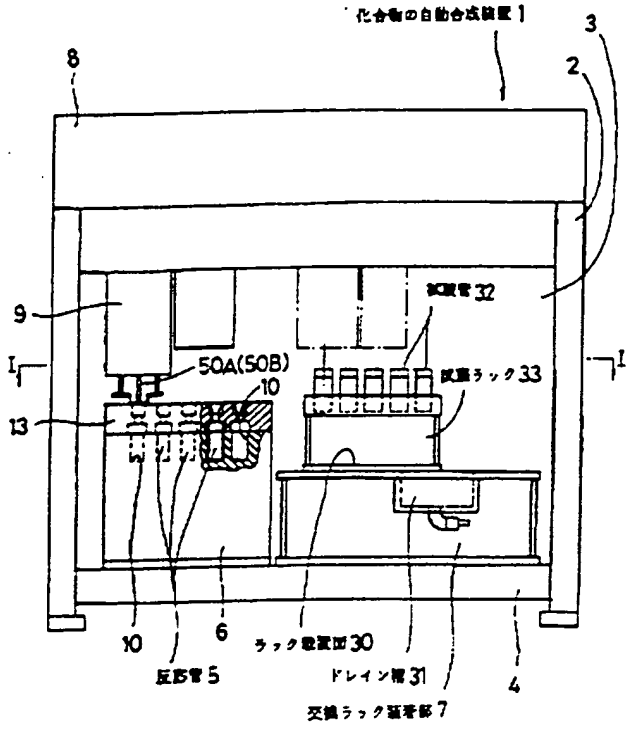
11

31・・・ドレイン槽　32・・・試験管
33・・・試薬ラック　34・・・試験管
35・・・サンプルラックカートリッジ　36・・・沪過カ
37・・・沪過ラック　38・・・抽出管
39・・・カラム精製ラック　43・・・試験管
44・・・フラクションラックラック　45・・・シフト

12

50A・・サンプリングニードル（薬液注入ニードル）
50B・・カラム精製ニードル（薬液注入ニードル）
56・・・透孔　57・・・シリコンゴム
58・・・ライニング　59・・・上端開口部
60・・・TLC基板　61・・・TLC基板支持ラック

【図1】



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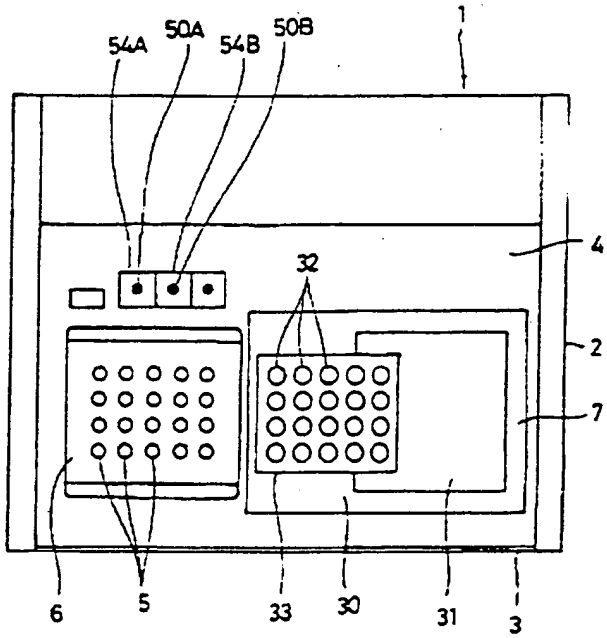

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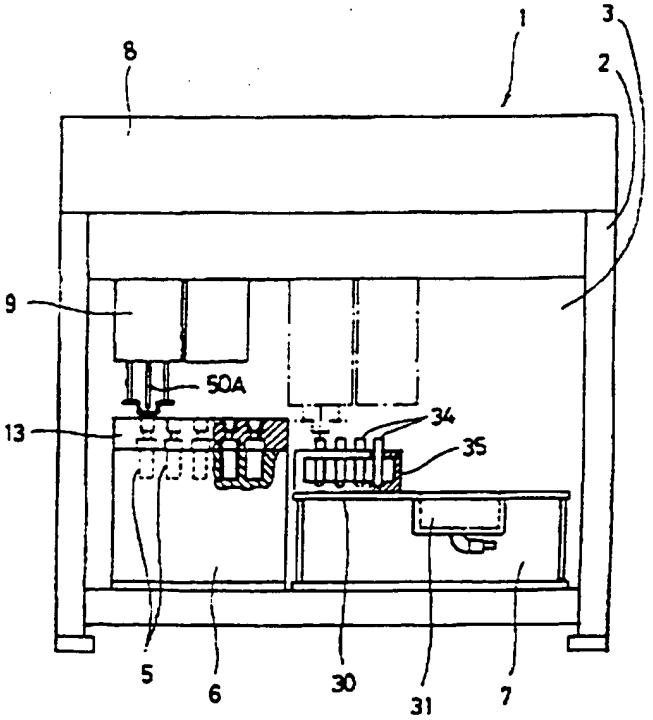

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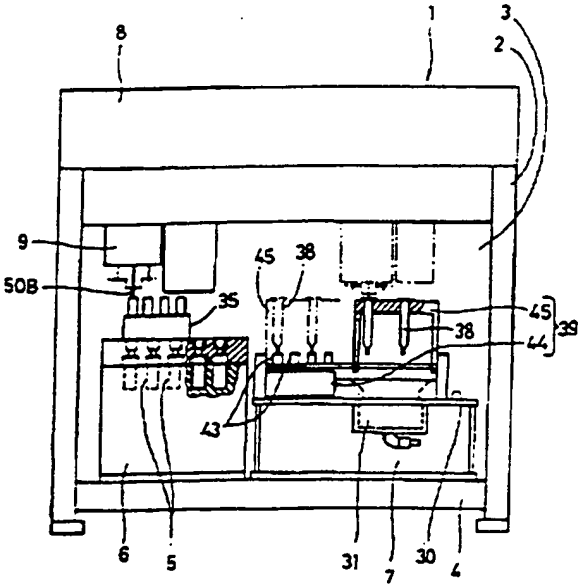

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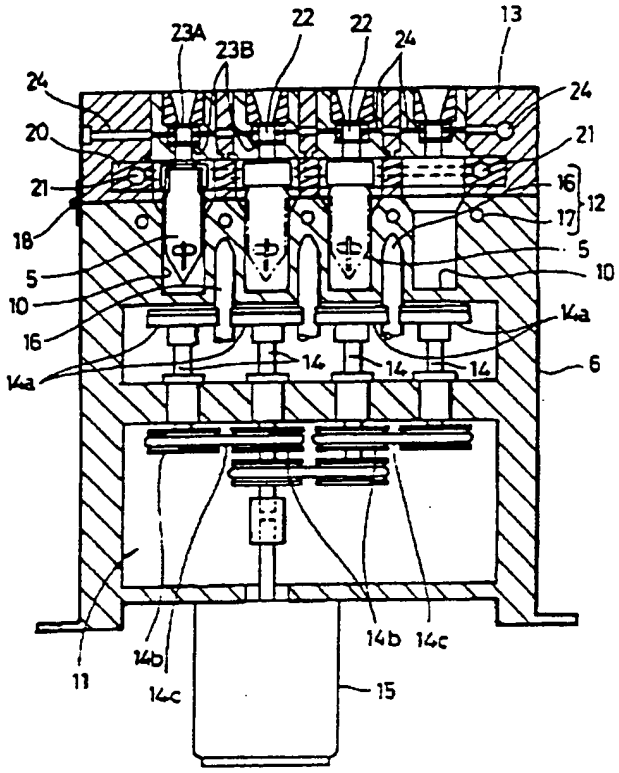
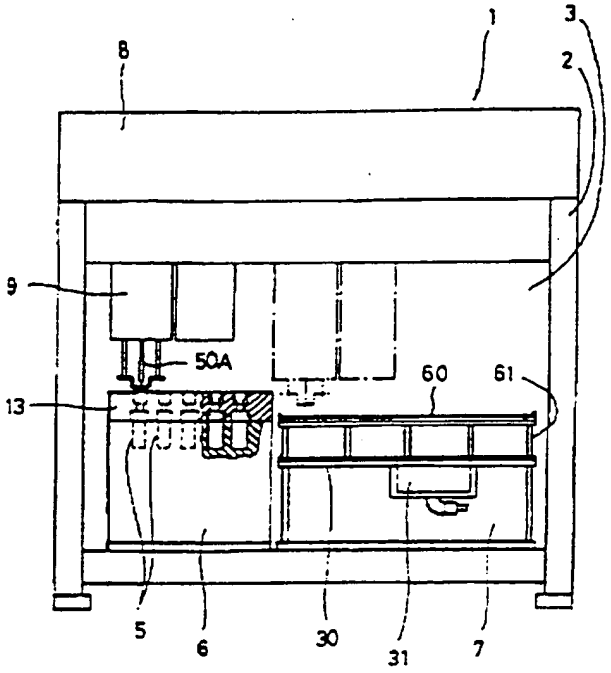

23A
23B
22
22
24
13
24
24
20
21
21
16
12
17
18
5
5
10
10
16
14a
14a
14
14
14
6
14b
14c
11
14b
14c
15

【図5】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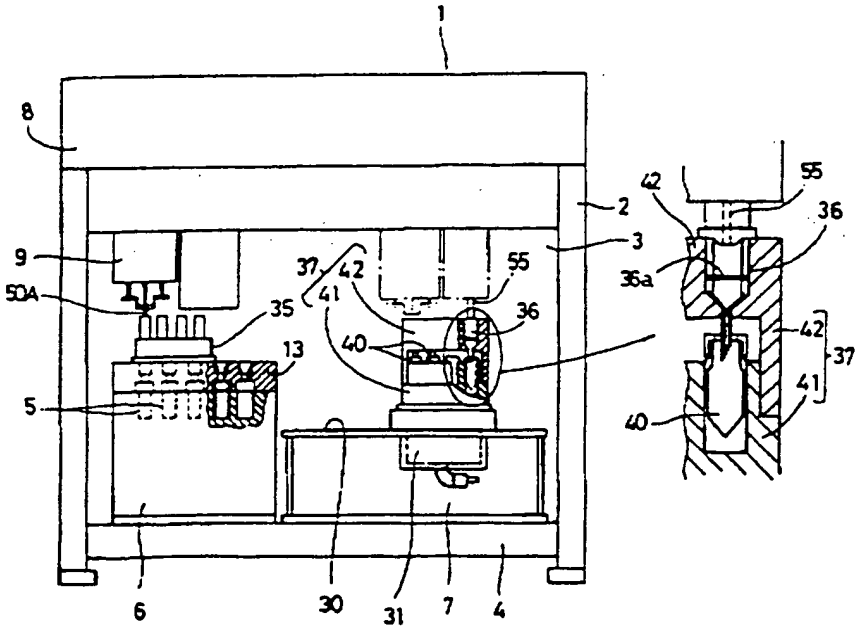
1
3
2
9
50A
60
61
13
5
6
30
31
7

【図6】


1
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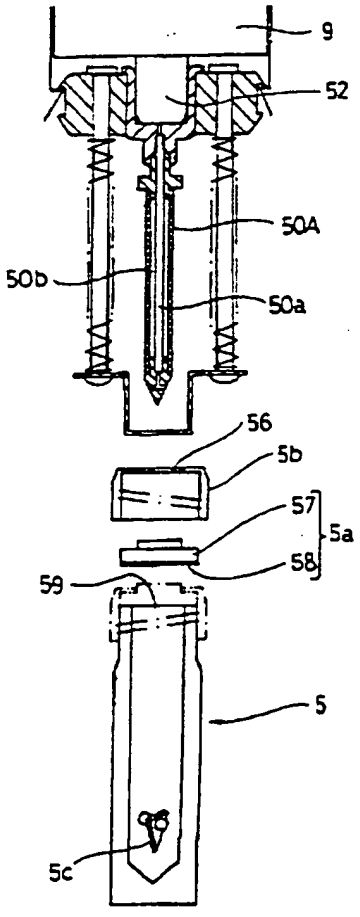
3
9
50A
35
37
42
41
55
36
13
40
5
6
30
31
7
4
42
55
36
36a
42
37
41
40

【図9】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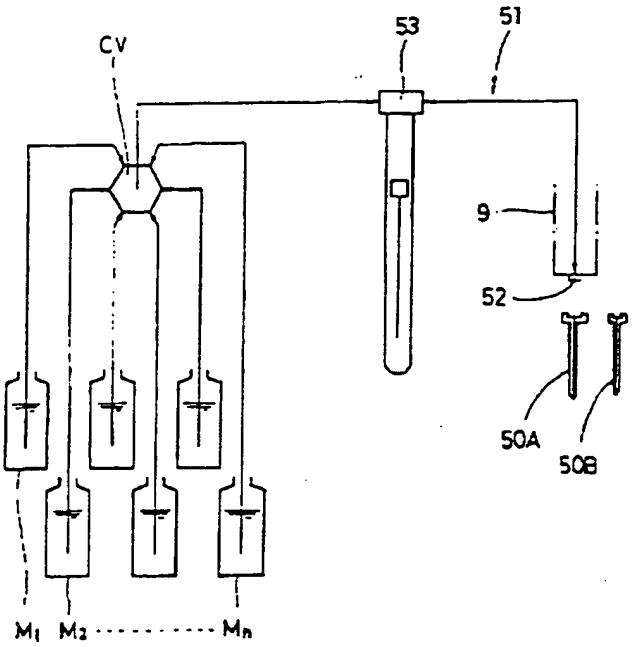
50A
50b
50a
56
5b
57
5a
58
59
5
5c

【図8】



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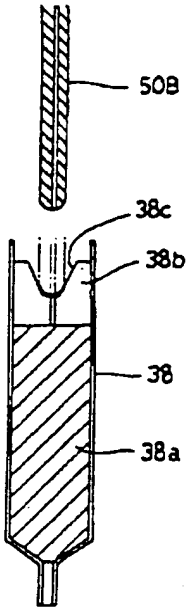

AN - 1998-433779 [37]
AP - JP19970238644 19970903
CPY - MORI-N
DC - J04
FS - CPI
IC - C07B61/00 ; C09K3/10
MC - J04-B
PA - (MORI-N) MORITEX KK
PN - JP10182501 A 19980707 DW199837 C07B61/00 009pp
PR - JP19960296181 19961108
XA - C1998-131156
XIC - C07B-061/00 ; C09K-003/10
AB - J10182501 In an automatic synthetic device (1) having chemicals injecting needles (50A,50B), which can be controlled to move between each test tube (32) arranged in a reagent rack (33) and each reaction tube (5) arranged in a reaction block (6) to absorb the reagents stored in each test tube (32) and to inject them into each reaction tube (5) in a specified quantity for synthesising compounds of any mixing ratios in each reaction tube (5). The reaction block (6) has a stirring device (11) to turn magnetic stirring pieces (5c) sunk in each reaction tube (5) for forming a rotary magnetic field to turn in the circumferential direction of each reaction tube (5), and a temperature control device (12) to heat or cool each reaction tube (5), the reagent rack (33) being mounted detachably on an exchange rack mounting part (7). The exchange rack mounting part (7) is formed so as to be able to mount, instead of the reagent rack (33), either a sample rack (35) having test tubes (34) being arranged to store a specified amount of compounds which have finished the reactions, a filtration rack (37) having filtration cartridges (36) being arranged to filter the compounds of a specified amount finished the reactions, or a column purification rack (39) having extraction tubes being arranged to make column purification of the compounds finished the reactions.
- ADVANTAGE - Various kinds of operations necessary for synthesizing compounds can be performed automatically. Further, the device is compact and simple to limit the installing space.
- (Dwg.1/10)
IW - AUTOMATIC SYNTHETIC DEVICE CHEMICAL INJECTION NEEDLE CAN CONTROL MOVE TEST TUBE REAGENT RACK
IKW - AUTOMATIC SYNTHETIC DEVICE CHEMICAL INJECTION NEEDLE CAN CONTROL MOVE TEST TUBE REAGENT RACK
NC - 001
OPD - 1996-11-08
ORD - 1998-07-07
PAW - (MORI-N) MORITEX KK
TI - Automatic synthetic device - having chemicals injecting needles which can be controlled to move between each test tube in a reagent rack

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			B
C 09 K 3/10		C 09 K 3/10	R

Request for Examination: Not yet submitted

Number of Claims: 6

(Total of 9 pages [in original])

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(74) Agent: Katsufumi Sawano, Patent Attorney, and one other

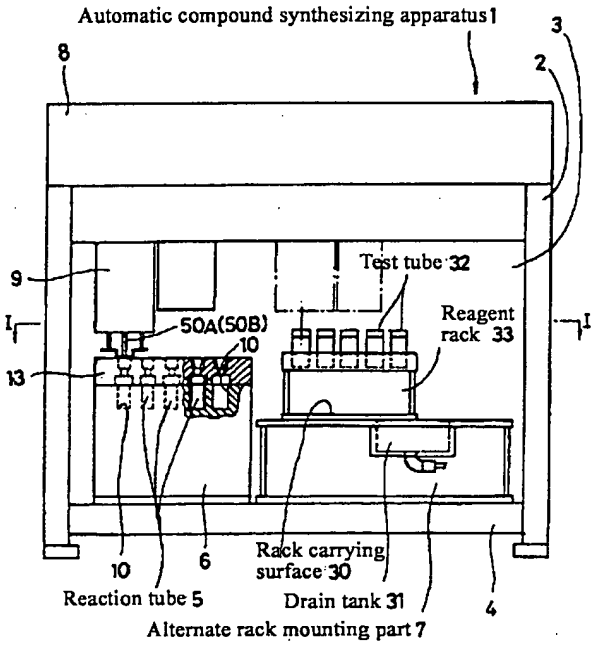
(54) [Title of the Invention]

AUTOMATIC COMPOUND SYNTHESIZING APPARATUS AND REACTION TUBE SEALING STRUCTURE USED IN THE SAME

(57) [Abstract]

[Object] The object of the present invention is to allow the automatic performance of various operations that are required in order to synthesize compounds, and also to make the construction of the apparatus extremely simple and compact so that the waste of installation space can be eliminated, and the manufacturing cost can be greatly reduced.

[Solution] [The apparatus of the present invention] is equipped with a chemical solution injection needle (50A) whose movement is controlled (in a manner that allows positioning) between an alternate rack mounting part (7) and a reaction block (6) equipped with an agitating means which forms a rotating magnetic field that causes a magnet (5c) sunk into each reaction tube (5) to rotate, and a temperature control means (12) which heats or cools each reaction tube (5); furthermore, the apparatus is arranged so that a reagent rack (33) in which test tubes (32) each containing a specified amount of a reagent are disposed, a sample rack (35) in which test tubes (34) each containing a specified amount of a compound whose reaction has been completed are disposed, a filtration rack (37) in which filter-equipped filtration cartridges (36) into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, and a column purification rack (39) in which extraction tubes (38) that the compounds whose reactions have been completed to column purification are disposed, can be alternately mounted on the aforementioned alternate rack mounting part (7).



[Claims]

[Claim 1] An automatic compound synthesizing apparatus which is characterized by the fact that in an automatic compound synthesizing apparatus in which reagents stored in respective test tubes (32) disposed in a reagent rack (33) are sucked in and injected in specified amounts into respective reaction tubes (5) disposed in a reaction block (6) by a chemical solution injection needle (50A, 50B) whose movement is controlled so that this chemical solution injection needle can be positioned in the positions of the aforementioned test tubes (32) and the positions of the aforementioned reaction tubes (5), the aforementioned reaction block (6) is equipped with an agitating means (11) which forms a magnetic field that rotates in the circumferential direction of each reaction tube (5) and thus causes a magnetic agitator (5c) sunk into each reaction tube (5) to rotate, and a temperature control means (12) which heats or cools each reaction tube (5), the aforementioned reagent rack (33) is detachably mounted on an alternate rack mounting part (7), and

the aforementioned alternate rack mounting part (7) is formed so that a sample rack (35) in which test tubes (34) each containing a specified amount of a compound whose reaction has been completed, a filtration rack (37) in which filter-equipped filtration cartridges (36) into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, or a column purification rack (39) in which extraction tubes (38) that subject the compounds whose reactions have been completed to column purification are disposed, can be mounted instead of the aforementioned reagent rack (33).

[Claim 2] The automatic compound synthesizing apparatus claimed in Claim 1, in which the temperature control means (12) of the aforementioned reaction block (6) consists of a heater (16) that heats each reaction tube (5), and a circulation passage (17) that causes the external circulation of a coolant that cools each reaction tube (5).

[Claim 3] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] in the aforementioned alternate rack mounting part (7), a drain tank (31) is formed on one side (left or right) of a rack carrying surface (30) that carries the rack.

[Claim 4] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] [i] in the aforementioned alternate rack mounting part (7), a drain tank (31) is formed on one side (left or right) of a rack carrying surface (30) that carries the rack, [ii] in the aforementioned column purification rack (39), a fraction rack (44) in which test tubes (43) that recover the eluate from the aforementioned extraction tubes (38) are disposed is carried on the portion of the aforementioned rack carrying surface (30) where there is no drain tank (31), and a shift rack (45) in which in the extraction tubes (38) that subject the samples whose reactions have been completed to column purification are disposed is installed so that this shift rack (45) can slide in the horizontal direction above the aforementioned fraction rack (44), and [iii] this shift rack (45) is formed so that it is positioned above the aforementioned fraction rack (44) when caused to slide to one end, and so that it is positioned above the drain tank (31) when caused to slide to the other end.

[Claim 5] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] the aforementioned alternate rack mounting part (7) is formed so that a TLC substrate supporting rack (61) which supports (in a substantially horizontal attitude) a TLC substrate (60) on which a fixed layer [Translator's note: possibly "fixing layer"] for thin-layer chromatography is formed can be mounted instead of the aforementioned reagent rack (33).

[Claim 6] A sealing structure which is characterized by the fact that aluminum caps (5b) in which through-holes (56) through which a chemical solution injection needle (50A, 50B) is passed are formed are screw-engaged with the upper-end opening parts (59) of reaction tubes (5) in which compounds with arbitrary mixture rates are synthesized by the injection of specified amounts of a plurality of reagents by the aforementioned [reagent injection] needle, elastic packing (5a) is interposed between these aluminum caps (5b) and the upper-end opening parts (59) of the reaction tubes (5), this elastic packing (5a) is formed from silicone rubber (57), and a lining (58) consisting of a fluororesin film is applied to the bottom surface of the packing (5a).

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention] The present invention relates to an automatic compound synthesizing apparatus which synthesizes compounds with arbitrary mixture rates in respective reaction tubes disposed in a reaction block, and a reaction tube sealing structure used in this automatic compound synthesizing apparatus.

[0002]

[Prior Art] Recently, a procedure known as combinatorial chemistry has been used in cases where novel compounds are created by combining several substances. In this procedure, a plurality of different types of reagents prepared beforehand are mixed at arbitrary mixture rates in respective test tubes, so that numerous samples with different mixture rates are synthesized, and compounds with optimal mixture rates are selected from these compounds. In concrete terms, various types of operations are necessary: namely, a reagent injection operation is first performed in which reagents are injected at arbitrary mixture rates into each of a large number of reaction tubs disposed in a rack. Then, a reaction operation is performed in which specified chemical reactions are caused to proceed by agitating the reagents that have been injected into the reaction tubes, and controlling the temperature. Then, in cases where the compounds synthesized by the completion of the reactions are separated into a plurality of liquid layers, a liquid separation operation is performed in which the compounds are sucked in from specified liquid layer portions, and in cases where it is necessary to filter the compounds whose reactions have been completed, a filtration operation is performed; furthermore, a column purification operation is performed in order to analyze the compounds whose reactions have been completed.

[0003] In such cases, extremely large numbers of samples are synthesized, and the abovementioned treatments must be performed for each of these samples. Recently, therefore, a procedure has been adopted in which these various treatments are performed automatically using a reagent injection apparatus, reaction apparatus, liquid separation

apparatus, filtration apparatus and column purification apparatus, etc. In such a procedure, reagents are first injected into the respective reaction tubes at specified mixture rates by the reagent injection apparatus. Next, in the reaction apparatus, since various conditions such as the temperature conditions, time conditions and agitation conditions, etc., under which the chemical reactions are performed are pre-programmed, reactions will proceed according to this program if the respective reaction tubes into which the reagents have been injected at specified mixture rates are set in the reaction apparatus. Then, in cases where the compounds whose reactions have been completed are separated into a plurality of liquid layers, the desired compounds can be extracted from specified portions of the liquid layers by treating these liquid layers with the liquid separation apparatus. If necessary, furthermore, the compounds inside the reaction tubes can be subject to an analysis pre-treatment by the column purification apparatus after being filtered by the filtration apparatus.

[0004]

[Problems to Be Solved by the Invention] However, in cases where such an automated apparatus is used, although the respective operations are automated, only one operation can be performed in each apparatus, so that an automated apparatus must be installed for each operation, thus leading to problems of increased cost and wasteful installation space. Furthermore, in cases where it is attempted to perform these respective operations using a single apparatus, the manufacturing cost is not greatly alleviated merely be concentrating the respective apparatuses [into a single unit], and the resulting apparatus is increased in size so that there is no saving in terms of installation space.

[0005] Accordingly, the technical object of the present invention is to make it possible to perform the various operations required for the synthesis of compounds automatically, and also to make the apparatus extremely compact, so that there is no waste of installation space, and so that the manufacturing cost can be greatly reduced.

[0006]

[Means Used to Solve the Abovementioned Problems] In order to solve the abovementioned problems, the present invention is characterized by the fact that in an automatic compound synthesizing apparatus in which reagents stored in respective reaction tubes disposed in a reagent rack are sucked in and injected in specified amounts into respective reaction tubes disposed in a reaction block by a chemical solution injection needle whose movement is controlled so that this chemical solution injection needle can be positioned in the positions of the aforementioned test tubes and the positions of the aforementioned reaction tubes, the aforementioned reaction block is equipped with an agitating means which forms a magnetic field that rotates in the circumferential direction of each reaction tube and thus causes a magnetic agitator sunk into each reaction tube to rotate, and a temperature control means which heats or cools each reaction tube, the aforementioned reagent rack is detachably mounted on an alternate rack mounting part, and the aforementioned alternate rack mounting part is formed so that a sample rack in which test tubes each containing a specified amount of a compound whose reaction has been completed, a filtration rack in which filter-equipped filtration cartridges into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, or a column purification rack in

which extraction tubes that subject the compounds whose reactions have been completed to column purification are disposed, can be mounted instead of the aforementioned reagent rack.

[0007] In the present invention, a reagent rack, a sample rack, a filtration rack and a column purification rack can be alternately mounted on the alternate rack mounting part. Accordingly, if the reagent rack is mounted in cases where a reagent injection operation is to be performed, the reagents contained in the respective test tubes of the reagent rack can be sucked in by the chemical solution injection needle and injected into the respective reaction tubes disposed in the reaction block. Next, since the reaction block is equipped with an agitating means which forms a rotating magnetic field that rotates magnets sunk into each reaction tube, and a temperature control means that heats or cools each reaction tube, a reaction operation can be performed which causes specified chemical reactions to proceed while agitating the reagents injected into the reaction tubes and controlling the temperature in this location.

[0008] Furthermore, in cases where a liquid separation operation is to be performed, it is sufficient to mount the sample rack on the alternate rack mounting part, to suck in the compounds from specified liquid phases in the reaction tubes by means of the chemical solution injection needle, and to discharge these compounds into the test tubes of the sample rack. Moreover, in cases where a filtration operation is to be performed, it is sufficient to mount the filtration rack on the alternate rack mounting part, and to discharge the compounds sucked in by the chemical solution injection needle from the reaction tubes disposed in the reaction block or the test tubes disposed in the sample rack carried on the reaction block into the filtration cartridges of the filtration rack. Furthermore, in cases where a column purification reaction is to be performed, it is sufficient to mount the column purification rack on the alternate rack mounting part, and to discharge the compounds sucked in by the chemical solution injection needle into the extraction tubes of the column purification rack. Thus, various operations can be performed automatically in a single apparatus, merely by exchanging the racks mounted on the alternate rack mounting part. Accordingly, the apparatus itself can be made extremely compact, and the manufacturing cost is also reduced.

[0009]

[Working Configurations of the Invention] A working configuration of the present invention will be concretely described below with reference to the attached figures. Figure 1 is a front view which shows the automatic compound synthesizing apparatus of the present invention. Figure 2 is a sectional view along line I-I in Figure 1. Figure 3 is an enlarged view which shows the internal structure of the reaction block. Figure 4 is a front view which shows the sample rack mounted on the alternate rack mounting part. Figure 5 is a front view which shows the TLC substrate supporting rack mounted on the alternate rack mounting part. Figure 6 is a front view which shows the filtration rack mounted on the alternate rack mounting part. Figure 7 is a front view which shows the column purification rack mounted on the alternate rack mounting part. Figure 8 is a fluid circuit diagram which shows the piping system. Figure 9 is an enlarged view which shows [one of] the reaction tubes and the sampling needle. Figure 10 is an enlarged view which shows [one of] the extraction tubes and the column purification needle.

[0010] In the automatic compound synthesizing apparatus of the present embodiment, a transparent door 3 is attached to the front of a box-form main body 2. When this door 3 is opened, a reaction block 6 in which reaction tubes 5, 5 with a volume of 5 cc are disposed is installed (for example) on the left front part of the base 4 of the main body 2, and an alternate rack mounting part 7 on which various types of racks can be detachably mounted is formed on the right front part [of the base 4]. Furthermore, a robot arm 9 whose movement is controlled in the directions of three orthogonal axes is disposed on the overhead part 8 of the main body, and can be positioned in the positions of the reaction tubes 5 disposed in the reaction block 6 or the positions of the test tubes disposed in the racks mounted on the alternate rack mounting part 7.

[0011] In the reaction tubes 5, caps 5b which have elastic packing 5a formed in a two-layer structure consisting of silicone rubber and a fluororesin film are mounted on the upper-end opening parts 59, and magnetic agitators 5c which have N and S poles formed on both ends are suck into the interiors of the reaction tubes 5. More concretely, an aluminum cap 5b in which a through-hole 56 through which the chemical solution injection needle 50A or 50B (described later) is passed is screw-engaged with the upper-end opening part 59 of [each] reaction tube 5, and elastic packing 5a is interposed between this aluminum cap 5b and the upper-end opening part 59 of the reaction tube 5. This elastic packing 5a is formed from a dimethylsilicone rubber which has a hardness HsA of approximately 20 to 25 as measured by a JIS-A type hardness testing machine, and a lining 58 consisting of a fluororesin film with a thickness of approximately 100 μm is applied to the bottom surface of the packing. For example, a tetrafluoroethylene-hexafluoropropylene copolymer film is used as this fluororesin film.

[0012] In the reaction block 6, accommodating holes 10 ... in which reaction tubes 5 with a volume of (for example) 5 cc are accommodated in the form of a matrix at a fixed spacing are opened in the upper surface, and the reaction block 6 is equipped with an agitating means 11 which forms a rotating magnetic field that rotates in the circumferential direction of the respective reaction tubes 5 and causes the rotation of magnetic agitators 5c that are sunk into the reaction tubes 5, and a temperature control means 12 which heats or cools the respective reaction tubes 5, in a state in which these reaction tubes 5 ... are accommodated in the respective accommodating holes 10 .... Furthermore, a cooling manifold 13 which cools the caps 5b of the reaction tubes 5 during heated reactions in a state in which the reaction tubes 5 are mounted is attached to the reaction block 6. Moreover, this reaction block 6 can be removed from the automatic synthesizing apparatus 1 if necessary.

[0013] In the agitation means 11, rotating shafts 14 which have permanent magnets 14a attached to their tip ends are disposed beneath the respective accommodating holes 10, and pulleys 14b are attached to the other ends of these rotating shafts 14. A plastic belt 14c is mounted on these pulleys 14b so that [the rotating shafts 14] can be rotationally driven by a motor 15. Furthermore, the temperature control means 12 consists of an electric heater 16 which heats the reaction tubes 5 accommodated in the accommodating holes 10, and a circulation passage 17 which allows the external circulation of a coolant that cools the respective reaction tubes 5. The heater 16 is powered, or a coolant is caused to flow through the circulation passage 17, in accordance with a set temperature.

[0014] Furthermore, the cooling manifold 13 is attached to the reaction block 6 via a hinge 18, so that the cooling manifold 13 can be opened and closed, and a cooling block 20 in which recesses 19 that cover the caps 5b of the respective reaction tubes 5 are formed is disposed on the bottom surface side of the manifold 13, and a circulation passage 21 which allows the external circulation of a coolant is formed in this cooling block 20. Furthermore, each of the aforementioned recesses 19 is opened on the upper surface side via a through-hole 22 into which the sampling needle (chemical solution injection needle, described later) is inserted. These through-holes 22 are closed off by two silicone rubber sheets 23A and 23B that are disposed with a specified spacing, and the spaces between the silicone rubber sheets in the respective through-holes 22 are connected via a nitrogen gas supply passage 24.

[0015] In the alternate rack mounting part 7, a rack carrying surface 30 which carries the various types of racks is formed, and a drain tank 31 is formed on one side (left or right) of this carrying surface 30. Furthermore, a reagent rack 33 in which a plurality of test tubes 32 that contain reagents are disposed, a sample rack 35 in which test tubes 34 that each contain a specified amount of a compound whose reaction has been completed are disposed, a filtration rack 37 in which filter-equipped filtration cartridges 36 into which specified amounts of compounds whose reactions have been completed are injected and filtered, a column purification rack 39 in which extraction tubes 38 that subject compounds whose reactions have been completed to column purification are disposed, and a TLC substrate supporting rack 61 which supports (in a substantially horizontal attitude) TLC substrates 60 that are used in thin-layer chromatography for the analysis of compounds during the reactions or compounds whose reactions have been completed, are formed so that these racks can be mounted on the rack carrying surface 30.

[0016] In the filtration rack 37, a cartridge rack 42 in which filtration cartridges 36 are disposed at the same pitch as test tubes 40 is detachably mounted on the upper surface of a rack main body 41 in which the abovementioned test tubes 40 are disposed, and the filtration cartridges 36 are formed so that only the filter parts 36a of these cartridges can be replaced.

[0017] In the column purification rack 39, a fraction rack 44 in which test tubes 43 are disposed is carried on the portion of the rack carrying surface 30 where there is no drain tank 31, and a shift rack 45 in which extraction tubes 38 that subject the compounds whose reactions have been completed to column purification are disposed is installed so that this shift rack 45 can slide in the horizontal direction above the aforementioned fraction rack 44. This shift rack 45 is formed so that it is positioned directly above the aforementioned fraction rack 44 when caused to slide to one end, and so that it is positioned directly above the drain tank 31 when caused to slide to the other end.

[0018] The TLC substrates 60 that are supported on the TLC substrate rack 61 are formed by (for example) kneading a powdered adsorbing agent such as silica gel, alumina or cellulose, etc., together with calcined gypsum, etc., and fixing this mixture to a glass substrate or aluminum substrate, thus forming a thin layer that acts as a fixed layer for thin-layer chromatography. Furthermore, the TLC substrates 60 may consist of a single large substrate that can be carried on the substrate supporting rack 61, or relatively small substrates formed by splitting such a large substrate into a plurality of substrates.

Furthermore, a single large substrate may be formed so that this substrate can be split if necessary.

[0019] Furthermore, a sampling needle (chemical solution injection needle) 50A which injects reagents into the reaction tubes 5 and sucks in reagents from the reaction tubes 5, and a column purification needle (chemical solution injection needle) 50B which injects compounds or solvents into the reaction tubes 38 when column purification is performed, can be alternately attached to the robot arm 9. This sampling needle 50A is formed with a pointed tip so that it can pierce the elastic packing 5a mounted in the cap 5b of each reaction tube 5; furthermore, a flow passage 50a which sucks in and injects reagents is opened in the tip end of the needle, and a discharge flow passage 50b which discharges the air inside the reaction tube 5 to the outside when the needle 50A has pierced [the packing] is opened in the lower end and upper end of the needle 50A. Furthermore, in cases where acidic reagents such as hydrochloric acid or sulfuric acid, etc., are injected as reagents, a sampling needle 50A is used in which at least the portions [of the needle] that form the flow passage 50a are formed by an acid-resistant metal such as Hastealloy C, etc. Furthermore, the tip end of the column purification needle 50B is formed with a spherical surface shape, so that this tip end adheres tightly to the recess 38c of the cap 38b that is inserted into the upper end of the corresponding extraction tube 38 filled with a filling agent 38a.

[0020] Furthermore, the robot arm 9 is equipped with a piping system 51 that sucks in or discharges reagents, and injects solvents. A port 52 which is connected to the aforementioned needle 50A or 50B is formed in one end of this piping system 51, and a plurality of solvent bottles M_1 through M_n are connected in a switchable manner to the other end of the piping system 51 via a switching valve CV. A digitally controlled syringe pump 53 is interposed as a flow rate controlling pump that can switch the direction of intake and discharge. Accordingly, using this sampling needle 50A, specified amounts of reagents can be sucked in from the test tubes 32 disposed in the reagent rack 33, and these reagents can be discharged in specified amounts into each of the reaction tubes 5 disposed in the reaction block 6. Furthermore, solvents from the solvent bottles M_1 through M_n can be discharged in specified amounts into each of the reaction tubes 5, and the compounds whose reactions have been completed in the reaction tubes 5 can be sucked in and discharged into the test tubes 34 disposed in the sample rack 35 or the filtration cartridges 36 disposed in the filtration rack 37. Furthermore, using the column purification needle 50B, specified amounts of specified solvents can be discharged into the extraction tubes 38 disposed in the column purification rack 39 from the solvent bottles M_1 through M_n, and compounds whose reactions have been completed can be sucked in and discharged in specified amounts.

[0021] Furthermore, 54A and 54B are needle holders that accommodate the aforementioned needles 50A and 50B. Cleaning devices (not shown in the figures) that blow a cleaning liquid or pressurized air onto the tip ends of the needles 50A and 50B are installed inside these holders. Furthermore, 55 indicates a multi-unit pressurizing nozzle that fills the interiors of the filtration cartridges 36 with nitrogen gas under pressure when filtration is performed.

[0022] The above is an example of the construction of the present invention; next, the operation of the present invention will be described. When compounds are synthesized,

for example, (1) a reagent injection operation, (2) a solvent injection operation, (3) a reaction operation, (4) a TLC analysis operation, (5) a liquid separation sampling operation, (6) a filtration operation, and (7) a column purification operation, are performed. Accordingly, these operations will be described.

[0023] The reagent injection operation is an operation in which reagents contained in the respective test tubes 32 disposed in the reagent rack 33 are sucked in an injected in specified amounts into each of the aforementioned reaction tubes 5 disposed in the reaction block 6 in order to synthesize compounds with arbitrary mixture rates in these reaction tubes 5. In this case, the reaction tubes 5 are first mounted in the accommodating holes 10 of the reaction block 6, after which the upper surface [of the reaction block 6] is covered by the cooling manifold 13. Meanwhile, the reagent rack 33 in which a plurality of test tubes 32 containing reagents are disposed is mounted on the alternate rack mounting part 7. In this state, when the reagent injection amounts are set for each reaction tube 5, the sampling needle 50A is mounted on the tip end of the robot arm 9, and the movement of this sampling needle is controlled so that the reagent in [one of] the aforementioned test tubes 32 is sucked in and discharged in specified amounts into each of the reaction tubes 5. Afterward, the sampling needle 50A is cleaned by the cleaning device inside the needle holder 54A. Next, the reagent in a different test tube 32 is discharged into each of the reaction tubes 5. This process is repeated so that reagents of the required types are injected into each of the reaction tubes 5 at an arbitrary mixture rate.

[0024] Next, a solvent injection operation is performed if necessary. This is an operation in which a specified amount of a solvent is discharged into each of the reaction tubes 5 in cases where it is necessary to use a solvent in the synthesis of the compound in question. In this case, required solvents from the respective solvent bottles M_1 through M_n are injected into each of the reaction tubes 5 using the sampling needle 50A. Here, furthermore, in cases where an acidic solvent such as hydrochloric acid or sulfuric acid, etc., is injected, an acid-resistant needle in which at least the internal flow passage 50a is formed from an acid-resistant metal is used as the sampling needle 50A.

[0025] After a plurality of reagents have thus been injected at arbitrary mixture rates into each of the reaction tubes 5, a reaction operation is performed. This is an operation in which a reaction is caused to proceed under preset conditions with specified temperature and time control by controlling the agitation and temperature. In cases where agitation is performed, starting the motor 15 of the agitation means 11 causes the permanent magnets 14a to rotate, so that a rotating magnetic field is formed in each accommodating hole 10, thus causing the magnetic agitator 5c that is sunk into each reaction tube 5 to rotate, so that the chemical solution in each reaction tube 5 is agitated. Furthermore, in cases where temperature control is performed, the heater 16 is powered if the set temperature is greater than room temperature, and a coolant supplied from the outside is circulated through the circulation passage 17 if the set temperature is lower than room temperature, so that a reaction is caused to proceed under specified temperature conditions.

[0026] Furthermore, in cases where the reaction tubes 5 are heated, there is a danger that the reaction solvent in the reaction tubes 5 will leak to the outside so that the concentration of the reaction solution changes. Accordingly, in this case, the spaces around the reaction tubes 5 are filled with nitrogen gas from the nitrogen gas supply

passage 24 formed in the cooling manifold 13, so that the reaction tubes 5 are placed in a nitrogen gas atmosphere. In this sate, a coolant is supplied to the circulation passage 21 so that the caps 5b of the reaction tubes 5 are cooled. In particular, if aluminum, which is superior in terms of thermal conductivity, is used as the material of the caps 5b, then the elastic packing 5a inside each reaction tube 5 and the vicinity of the upper-surface opening part 59 can be cooled by cooling the caps 5b. As a result, the reaction solvent that is evaporated inside the reactions tubes 5 is cooled by the caps 5b so that this reaction solvent condenses and is returned to the interiors of the reaction tubes 5. Accordingly, there is no change in the concentration of the reaction solution inside the reaction tubes 5. Furthermore, since the reaction tubes 5 are placed in a nitrogen gas atmosphere, there is no condensation around the reaction tubes 5, especially on the caps 5b, and even if some condensation should occur, the upper-surface opening parts 59 are closed off in an air-tight state by the elastic packing 5a, so that water droplets do not enter the interiors of the reaction tubes 5. Moreover, when an experiment was performed in which the elastic packing 5a of the present example in which a lining 58 consisting of a fluororesin film was formed on the bottom surface of a silicone rubber [part] 57, and 100% methanol was placed in the reaction tubes 5 and heated for 24 hours while the caps 5b were cooled, the amount of decrease in the contents of the reaction tubes was approximately 0.18% on the average, thus confirming that extremely good sealing characteristics can be obtained.

[0027] Next, at the point in time where the reaction is completed, a reaction stopping agent (e. g., water) is injected so that the progress of the reaction is halted. Then, if necessary, a TLC analysis operation using thin-layer chromatography is performed in order to check whether or not the desired compound has been purified, and in some cases, such an operation is performed before the reaction is completed in order to check the composition during the reaction. This TLC analysis operation is especially useful for checking which liquid layer contains the purified target compound in cases where the synthesized compound is separated into a plurality of liquid layers. In concrete terms, the reagent rack 33 is removed, the TLC substrate supporting rack 61 is mounted, and specified amounts of the compound are dropped onto the TLC substrates 60 supported on this rack 61 from the respective liquid layers, and are then developed on the TLC substrates 60, after which an analysis is performed by irradiation with ultraviolet radiation, etc.

[0028] Then, the desired compound synthesized in each reaction tube 5 is removed. In this case, the reagent rack 33 or TLC substrate supporting rack 61 mounted on the alternate rack mounting part 7 is first removed, and the sample rack 35 is mounted. Here, in cases where the compounds synthesized in the reaction tubes 5 are colloidal, and are not separated into liquid layers, there is no need to determine the positions of liquid layers; accordingly, it is sufficient in such cases merely to suck in the compounds in the reaction tubes 5 by means of the sampling needled 50A. On the other hand, in cases where the synthesized compounds are separated into a plurality of liquid layers, liquid layer sampling is performed, and the chemical solution in the liquid layer portion in which the target compound is purified is collected. This is accomplished by setting the position of the liquid layer inside the reaction tube 5, positioning the tip end of the sampling needle 50A inside this liquid layer and sucking in the compound, and

discharging the sucked-in compound into one of the test tubes 34 in the sample rack 35. This operation is performed for each reaction tube 5.

[0029] Furthermore, in cases where it is necessary to filter the compounds whose reactions have been completed, the filtration rack 37 is mounted so that it is positioned directly above the drain tank 31 of the alternate rack mounting part 7. Then, in cases where the compounds collected in the test tubes 34 of the sample rack 35 are to be filtered, the sample rack 35 is mounted on the reaction block 6, and the compounds in the test tubes 34 are sucked in and injected into the filtration cartridges 36 by means of the sample needle 50A. On the other hand, in cases where the compounds are injected directly into the filtration cartridges 36 from the reaction tubes 5, the compounds in the reaction tubes 5 are sucked in and injected into the filtration cartridges 36 by means of the sample needle 50A. Next, if necessary, the filtration time can be shortened by using the multi-unit pressurizing nozzle 55 to supply pressurized nitrogen gas to the filtration cartridges 36.

[0030] Furthermore, in cases where a column purification operation is to be performed as a pre-treatment for the structural analysis of the synthesized compounds, the column purification rack 39 is mounted on the alternate rack mounting part 7. In this case, test tubes 43 are first accommodated in the fraction rack 44, extraction tubes 38 are accommodated in the shift rack 45, and this shift rack 45 is caused to slide to the side of the drain tank 31. In this state, the column purification needle 50B is mounted on the tip end of the robot arm 9, and conditioning is performed by injecting a specified solvent into the respective extraction tubes 38.

[0031] Next, when conditioning is completed, sample loading is performed in which the samples sucked in from the sample rack 35 mounted on the reaction block 6 are injected into the respective extraction tubes 38. In this case, each time that one sample is injected into one extraction tube 38, the tip end of the column purification needle 50B is cleaned by the cleaning device inside the needle holder 54B so that the mixing of samples is prevented.

[0032] When sample loading is completed, a cleaning operation which washes away foreign matter held in the fixed layers of the extraction tubes 38 is performed. This is accomplished by injecting a cleaning solvent by means of the column purification needle 50B; in this case, the liquid that flows out of the extraction tubes 38 is recovered in the drain tank 31.

[0033] When the cleaning operation is completed, the shift rack 45 is caused to move to the side of the fraction rack 44, and a specified solvent is injected into the extraction tubes 38 so that the eluates are recovered in the respective test tubes 43 of the fraction rack 44, thus completing the column purification operation. In this case, furthermore, instead of recovering the eluates from the extraction tubes 38 directly in the respective test tubes 43, it would also be possible to monitor the eluates by means of an ultraviolet absorption meter so that the concentrations of the eluates or substances contained in the eluates are detected, and to move the fraction rack 44 and automatically change the test tubes 43 to new test tubes 43 each time there is a change in the detected substance or concentration, so that an automatic fractionation is performed with only the ultraviolet absorption peaks taken as fractions. Furthermore, the eluates recovered in the respective

test tubes 43 of the fraction rack 44 can be concentrated in a centrifugal separator, and after these concentrates are dissolved, a structural analysis can be performed using a structural analysis device.

[0034]

[Merits of the Invention] In the present invention, as was described above, respective operations required for the parallel synthesis of compounds, such as a reagent injection operation, a synthesizing reaction operation, a liquid separation sampling operation, a filtration operation and a column purification operation, etc., can be automatically performed using a single apparatus merely by replacing racks mounted on an alternate rack mounting part, so that the following superior merits are obtained: namely, the apparatus itself can be made extremely compact, and the manufacturing cost can be reduced.

[Brief Description of the Drawings]

[Figure 1] Figure 1 is a front view which shows the automatic compound synthesizing apparatus of the present invention.

[Figure 2] Figure 2 is a sectional view along line I-I in Figure 1.

[Figure 3] Figure 3 is an enlarged view which shows the internal structure of the reaction block.

[Figure 4] Figure 4 is a front view which shows the sample rack mounted on the alternate rack mounting part.

[Figure 5] Figure 5 is a front view which shows the TLC substrate supporting rack mounted on the alternate rack mounting part.

[Figure 6] Figure 6 is a front view which shows the filtration rack mounted on the alternate rack mounting part.

[Figure 7] Figure 7 is a front view which shows the column purification rack mounted on the alternate rack mounting part.

[Figure 8] Figure 8 is a fluid circuit diagram which shows the piping system.

[Figure 9] Figure 9 is an enlarged view which shows [one of] the reaction tubes and the sampling needle.

[Figure 10] Figure 10 is an enlarged view which shows [one of] the extraction tubes and the column purification needle.

[Explanation of Symbols]

1 Automatic compound synthesizing apparatus

5 Reaction tubes

5a Elastic packing

5b Cap

5c Magnetic agitator

6 Reaction block

7 Alternate rack mounting part

11 Agitating means

12 Temperature control means

16 Heater

17 Circulation passage

30 Rack carrying surface

31 Drain tank

32 Test tubes

33 Reagent rack

34 Test tubes

35 Sample rack

36 Filtration cartridges

37 Filtration rack

38 Extraction tubes

39 Column purification rack

43 Test tubes

44 Fraction rack

45 Shift rack

50A Sampling needle (chemical solution injection needle)

50B Column purification needle (chemical solution injection needle)

56 Through-hole

57 Silicone rubber

58 Lining

59 Upper-end opening part

60 TLC substrates

61 TLC substrate supporting rack

Figure 1

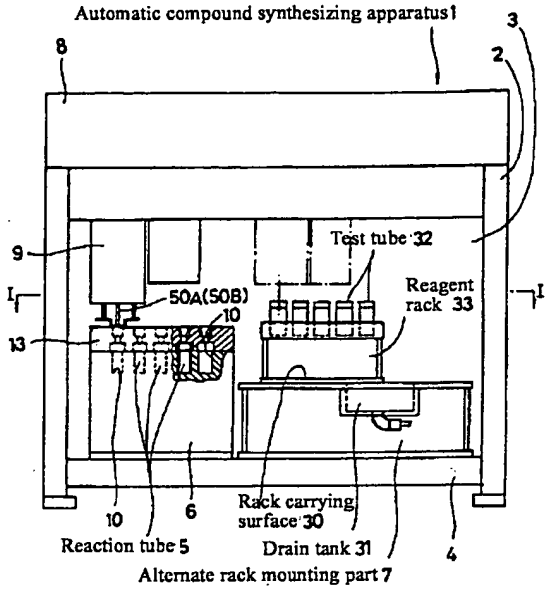


Figure 2

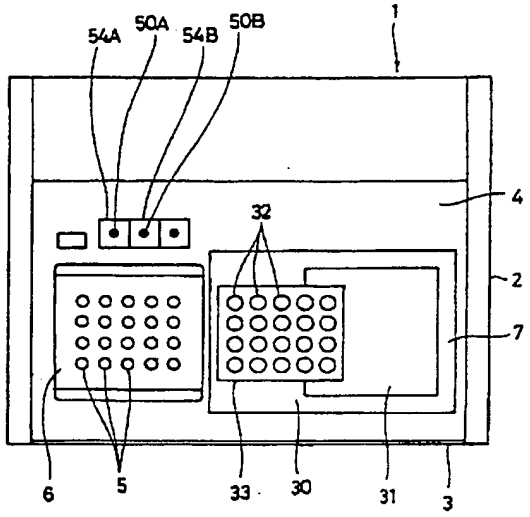


Figure 4

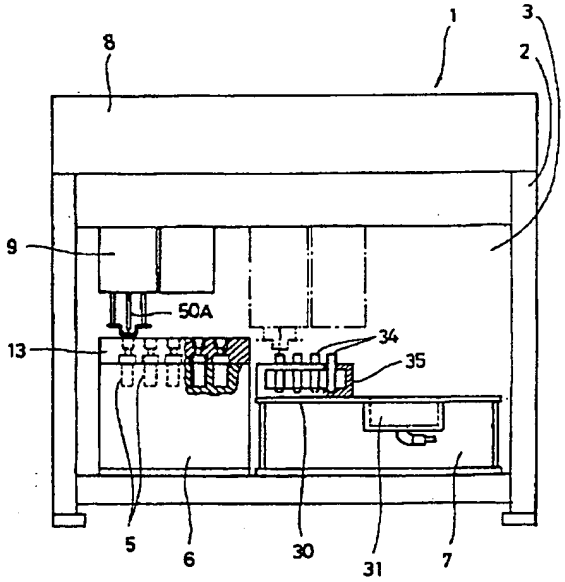


Figure 7

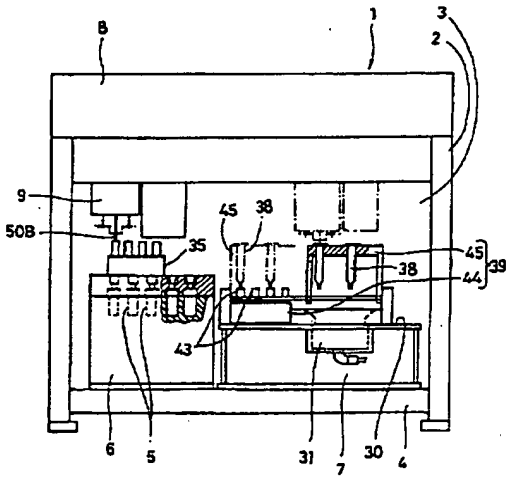


Figure 3

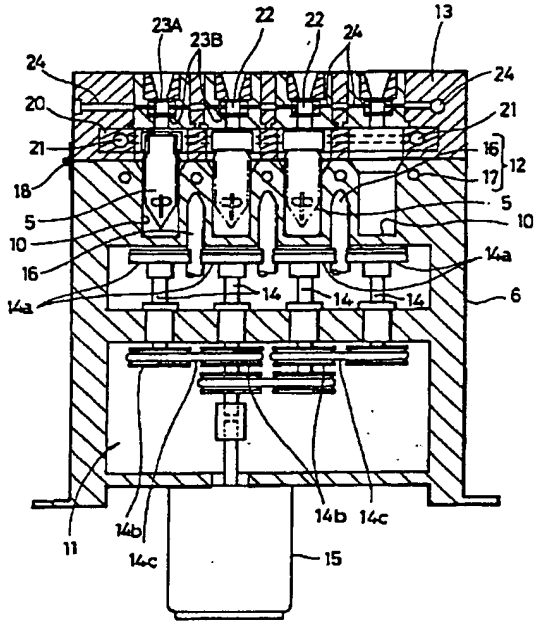


Figure 5

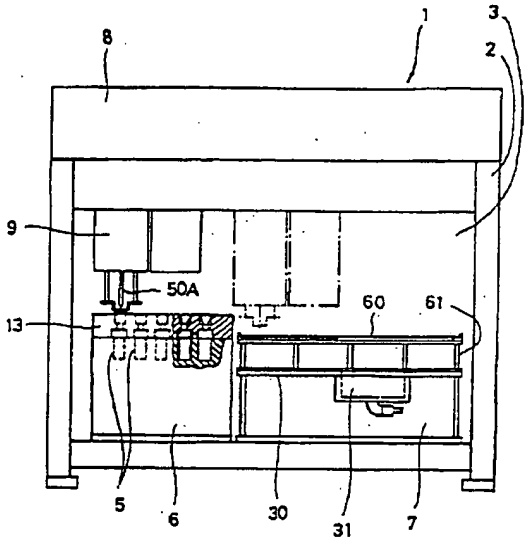


Figure 9

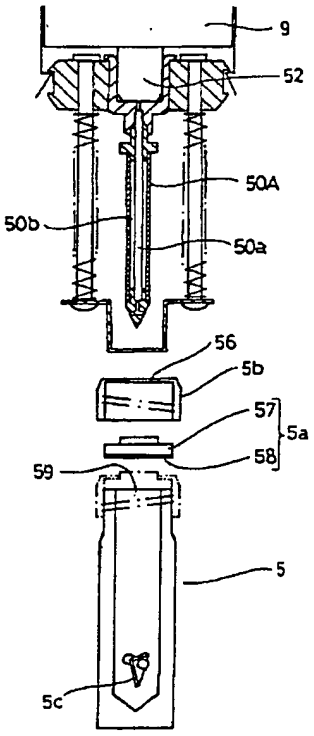


Figure 6

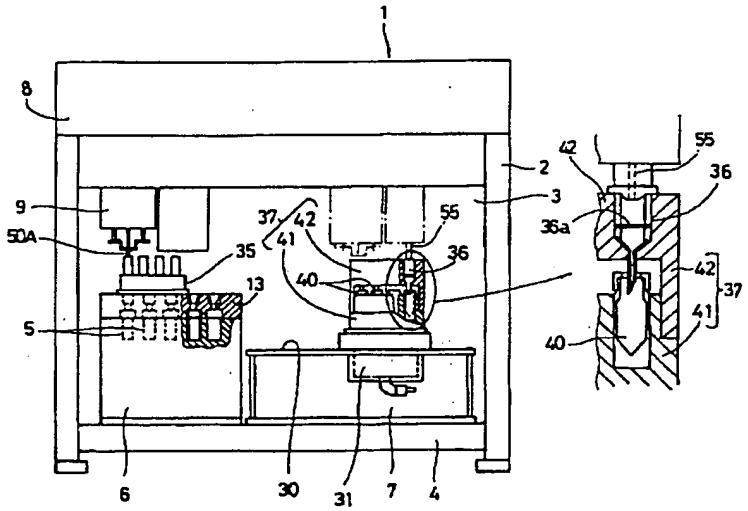


Figure 8

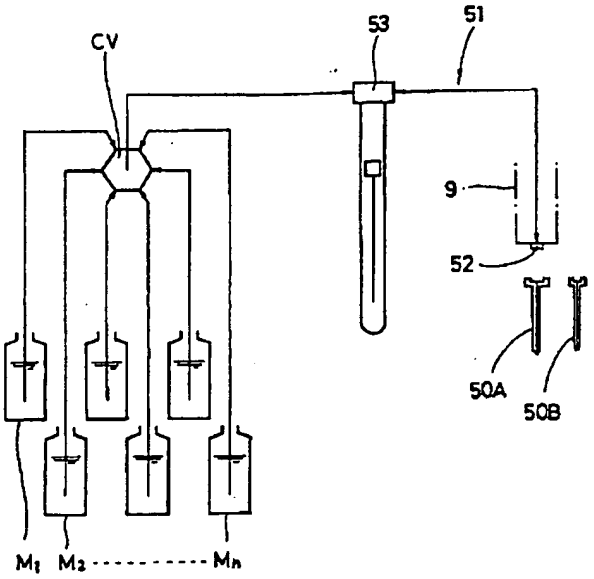


Figure 10